111/B 1000.00

#5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,739,101

Attn: Box Patent Ext.

Inventors: JEAN-PIERRE BOURGOGNE
ROLAND SORNAY

Assignee: FOURNIER INNOVATION ET SYNERGIE

REQUEST FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

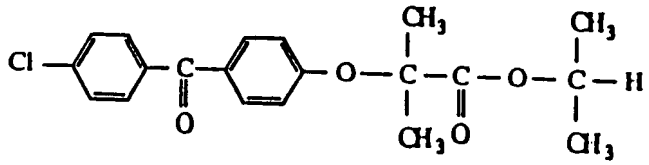
Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Fournier Innovation et Synergie, assignee of U.S. Patent No. 4,739,101 by an assignment from the inventors to Societe de Recherches Industrielles recorded on April 27, 1987, Reel 4701, Frame 0198, and from Societe de Recherches Industrielles recorded on December 4, 1987, in Reel 4798, Frame 0903, hereby requests an extension of the patent term for said patent.

040 TD 03/08/94 4739101 2 111 1,000.00 CK

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and follows the numerical format and headings set forth in 37 C.F.R. § 1.740:

1. A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

LIPIDIL (fenofibrate capsules) is a lipid regulating agent. It is available as capsules for oral administration. Each capsule contains 100 mg of fenofibrate. Each capsule also contains lactose, NF; magnesium stearate, NF; and pregelatinized starch, NF. The chemical name is 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid 1 methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}C1O_4$ and the molecular weight is 360.84; fenofibrate is insoluble in water.

The melting point is 77-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

2. A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 355. Section 505 provides for the submission and approval of new drug applications (NDAs).

3. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Fenofibrate was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on December 31, 1993. A copy of the letter from FDA announcing that approval is attached as Exhibit I.

4. An identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The only active ingredient in the approved product is Fenofibrate. Fenofibrate has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on December 31, 1993, and the last day within the sixty-day period permitted for submission of an application for extension of a patent is March 1, 1994. The date of submission of the present application is no later than March 1, 1994 and, therefore, the present application has been timely filed.

6. A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: JEAN-PIERRE BOURGOGNE
ROLAND SORNAY

U.S. Patent No. 4,739,101

Date of Issue: April 19, 1988

Date of Expiration: April 19, 2005.

7. A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the patent is attached as Exhibit II.

8. A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

No disclaimer, certificate of correction, or reexamination certificate were issued in this patent. A copy of the receipt of maintenance fee payment is enclosed as Exhibit III.

9. A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product.

U.S. Patent No. 4,739,101 claims the method of manufacturing the approved product, fenofibrate, in claim 8.

This claims read as follows:

> 8. The method according to claim 1 for the preparation of fenofibrate, wherein:
>
> (a) about 1 mol of VI in which R sub 1 is the 4-chlorobenzoyl group is reacted with about 2 mol of V in which R sub 2 is the isopropyl group, in the absence of a solvent and in the presence of about 1 mol of K sub 2 CO sub 3, at a temperature of about 140 degree(s) C. to about 145 degree(s) C., for about 5 hours.
>
> (b) after the addition of aqueous isopropanol to the resulting reaction medium, the excess K sub 2 CO sub 3 is neutralized with sulfuric acid at a temperature of the order of 100 degree(s) C.,
>
> (c) the resulting reaction medium is cooled to a temperature of between 15 and 25 degree(s) C. and the precipitate of fenofibrate is collected by filtration,
>
> (d) the precipitate filtered off in this way is washed with sodium hydroxide followed by water, and then
>
> (e) the fenofibrate is recrystallized from aqueous isopropanol.

10. A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent that claims a human drug product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved.

The Investigational New Drug Application (IND 19-056) for use of fenofibrate in the regulation of lipids was filed with the Food and Drug Administration (FDA) by Laboratories Fournier on July 17, 1981, and became effective on August 16, 1981.

The New Drug Application (NDA 19-304) was submitted on June 4, 1984 by Laboratories Fournier.

The New Drug Application (NDA 19-304) was approved by the FDA on December 31, 1993.

11. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The following are significant activities undertaken by the marketing applicant during the regulatory review period:

July 17, 1981	Filing of IND 19,056
1981 - 1984	Completion of clinical trial
June 4, 1984	Submisssion of NDA 19-304 (dated May 31, 1984) to the FDA
October 3, 1984	Meeting with FDA reviewing division concerning NDA
July 23, 1985	Meeting with FDA concerning FDA request for an additional study
September 30, 1985	FDA letter finding NDA as currently submitted not approvable
October 23, 1985	Submission of revised protocols for additional studies to FDA
November 14, 1985	Meeting with FDA reviewing division to discuss requirements for approval
March 21, 1986	FDA reviewing division letter stating that NDA deemed withdrawn for administrative purposes but that information in the original submission will be retained and can be referenced in a resubmission
July 8, 1986	Meeting with FDA BioPharmaceutics staff to discuss issues related to NDA

January 28, 1987	Meeting with FDA reviewing division to discuss issues related to clinical data in NDA
April 27, 1987	Resubmission of NDA
August 17, 1987	Submission of results of additional clinical study
June 21, 1988	Submission of safety update
June 9, 1989	Submission of safety update
June 29, 1989	Presentation to FDA Advisory Committee
August 14, 1989	Submission of draft carton and container labels
November 17, 1989	Meeting with FDA reviewing division concerning FDA request for a dose-ranging study
October 25, 1990	Meeting with FDA reviewing division concerning NDA
March 22, 1991	Submission of dose-ranging study protocol to FDA for review
June 25, 1992	Meeting with FDA reviewing division concerning NDA
November 12, 1993	Submission of draft package insert

The above listing is representative of the applicant's continuous contacts with the FDA concerning this Application. The approval letter for the NDA, attached as Exhibit I, recites 120 amendments to the NDA submitted by the applicant, dating from October 26, 1984 to November 12, 1993.

12. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Applicant is of the opinion that U.S. Patent No. 4,739,101 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

(a) U.S. Patent No. 4,739,101 claims a method of manufacturing a product, i.e., fenofibrate (35 U.S.C. § 156(a)).

(b) The term of U.S. Patent No. 4,739,101 has not expired (35 U.S.C. § 156(a)(1)).

(c) The term of U.S. Patent No. 4,739,101 has never been extended before submission of this application (35 U.S.C. § 156(a)(2)).

(d) This application is being submitted by the authorized agent of the owner of record of the patent in accordance with the requirements of 35 U.S.C. § 156(d) and the rules of the U.S. Patent and Trademark Office (35 U.S.C. § 156(a)(3)).

(e) The product, fenofibrate, has been subjected to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156(a)(4)).

(f) The commercial marketing or use of the product after the regulatory review period will be the first permitted commercial marketing or use of the product under Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355 (35 U.S.C. § 156(a)(5)(A)).

(g) No other patent has been extended for the same regulatory review period for the product, fenofibrate (35 U.S.C. § 156(c)(4)).

The length of extension of the patent term for U.S. Patent No. 4,739,101 claimed by Applicant is

2 years and 256 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775, as follows:

(a) Pursuant to 37 C.F.R. §1.775(c) the regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on August 16, 1981, and ended on December 31, 1993, which is a total of 4521 days or twelve years and 138 days. This is the sum of the two phases described below:

(i) The "Testing Phase" under 35 U.S.C. § 156(g)(1)(B)(i) began on August 16, 1981, and ended on June 4, 1984, which is 1024 days or two years and 293 days; and

(ii) The "Application Phase" under 35 U.S.C. § 156(g)(1)(B)(ii) began on June 4, 1984, and ended on December 31, 1993, which is 3497 days or nine years and 210 days.

(b) Pursuant to 37 C.F.R. § 1.775(d), the length of the patent term extension is calculated as follows:

(1) The number of days computed as follows is subtracted from the regulatory review period:

(i) The number of days in the regulatory review period which were on or before the date on which the patent was issued, April 19, 1988, which is 2439 days, and

(ii) The number of days during which Applicant did not act with due diligence, which is zero (0) days, and

(iii) One-half the number of days remaining in the Testing Phase after subtracting the days in the previous two subparagraphs, which is zero (0) days;

(2) This total of 2082 days, when added to the original term of the patent, which expires April 19, 2005, would result in the date December 31, 2010;

(3) Fourteen (14) years, when added to the date of NDA approval, December 31, 1993, would result in the date December 31, 2007;

(4) The earlier date of those in paragraphs (2) and (3) above is December 31, 2007.

(5) Because the patent was issued after September 24, 1984, one must add 5 years to the expiration date, leading to the date April 15, 2010.

(6) The earlier date of those in paragraphs (4) and (5) is December 31, 2007, and thus that is the date to which the patent term should be extended.

Therefore, Applicant is requesting an extension of 2 years and 256 days.

13. A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14. The prescribed fee for receiving and acting upon the application for extension.

A check in the amount of $1000 is enclosed with this application.

15. The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Dr. Max Fogiel
61 Ethel Road West
Piscataway, NJ 08854
908/819-8880

16. A duplicate of the application papers, certified as such.

A certified copy is submitted herewith.

17. An oath or declaration as set forth in paragraph (b) of 37 C.F.R. § 1.740.

I, MAX FOGIEL, hereby declare that:

1) I am a patent agent authorized to practice before the United States Patent and Trademark Office (Registration No. 19,170) and I have general authority from Fournier Innovation et Synergie, owner of U.S. Patent No. 4,739,101, to act on its behalf in patent matters;

2) I have reviewed and understand the contents of this application;

3) I believe that the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

4) I believe that an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

5) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,739,101.

Respectfully submitted,

FOURNIER INNOVATION ET SYNERGIE

By: Max Fogiel
MAX FOGIEL

Date: 2/25/94

EXHIBIT I

NDA APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-304

DEC 31 1993

Fournier Research Inc.
Attention: Mr. R. Lance Boyette
689 Mamaroneck Avenue
P.O. Box 340
Mamaroneck, NY 10543

Dear Mr. Boyette:

Please refer to your New Drug Application (NDA) dated May 30, 1984, and your resubmission dated April 29, 1987, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Lipidil (fenofibrate) Capsules (100 mg).

We acknowledge receipt of your amendments dated October 26, 1984, and January 29, March 27, May 1, June 25, July 1, July 25, August 22, October 10, and November 7 (2), 1985; March 25, May 20, May 31, July 22, August 3, August 29, September 15, and November 14, 1986; January 20, February 20 and 28, April 29, July 29, August 4, 5, and 17, October 1 and 14, November 4, 6 (2), 17 and 23, and December 1, 1987; February 12, 17 (2), and 24 (2), March 22, April 20, May 18, June 7, 21, 28, September 9, October 3 (3), and December 6, 1988; January 11, March 14, April 7, May 1 and 25, June 2 (2), 6 (2), 7, 9, 14, and 22, August 14, September 13, October 20, 23, 25, and 30, and November 3 and 13, 1989; January 3 (2) and 16, March 1, 5, and 22, April 20, August 27, September 11, October 8, November 15, 1990; January 29, March 22, May 27, June 18, August 23, December 2, 1991; January 13, February 12, 19, 26, April 6 and 24, May 8 and 27, June 15, July 24 and 30, august 17, October 12, November 6 (2), 16, and 25, December 1, 7, 9, 15, 18, and 28, 1992; May 18, June 10, 22, and 29, July 9, August 24 and 26, and November 12, 1993.

This NDA provides for the use of Lipidil as adjunctive therapy to diet for the treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who are at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.

We have completed the review of this application, as amended, including the revised draft physician insert (PI) labeling submitted November 12, 1993, and the draft carton and container labels submitted August 14, 1989, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft PI labeling submitted November 12, 1993. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) for the PI must be identical to the November 12, 1993, draft labeling and the August 14, 1989, draft carton and container labels. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. For administrative purposes this submission should be designated "FPL for approved NDA 19-304." Approval of this labeling by FDA is not required before it is used.

We note your November 12, 1993, commitments to the following post-approval actions:

1. To complete and file the results of the dose finding studies described in Protocols FEN 8906 and FEN 9107.

2. To conduct, complete, and file the results of the long-term study of fenofibrate in patients with established coronary artery disease, using angiographic end points of effectiveness as described in Protocol FEN 9122 (final protocol submitted November 12, 1993).

3. To develop a new dosing form of fenofibrate approximately equivalent to 50 mg of the present formulation and to study that form to determine its safety and effectiveness.

We request that you describe all submissions relating to these commitments as "Phase 4 commitments for NDA 19-304."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Mr. Stephen T. Trostle
Consumer Safety Officer
Telephone: 301-443-3520.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II, HFD-500
Center for Drug Evaluation and Research

EXHIBIT II

COPY OF PATENT

United States Patent [19]

Bourgogne et al.

[11] **Patent Number: 4,739,101**

[45] **Date of Patent: Apr. 19, 1988**

[54] METHOD FOR THE PREPARATION OF FIBRATES

[75] Inventors: **Jean-Pierre Bourgogne, Longvic; Roland Sornay, Ruffey les Echirey, both of France**

[73] Assignee: **Fournier Innovation et Synergie, Paris, France**

[21] Appl. No.: **43,184**

[22] Filed: **Apr. 27, 1987**

[30] **Foreign Application Priority Data**

Apr. 30, 1986 [FR] France 86 06258

[51] Int. Cl.[4] C07C 69/76

[52] U.S. Cl. 560/61; 560/62; 560/45

[58] Field of Search 560/61, 62, 45

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,759,950	9/1973	Grant	560/61
3,795,691	3/1974	Douglas	560/61

FOREIGN PATENT DOCUMENTS

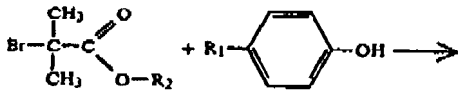
EP82413	6/1983	European Pat. Off.	560/61
EP128658	12/1984	European Pat. Off.	560/61
2060573	6/1971	Fed. Rep. of Germany	560/61

Primary Examiner—Paul J. Killos

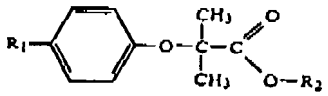
Attorney, Agent, or Firm—Max Fogiel

[57] **ABSTRACT**

The present invention relates to a method for the preparation of fibrates of the formula I according to the mechanism:



(V) (VI)



(I)

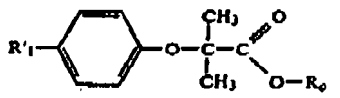
in which R_1 represents especially a halogen atom (in particular F, Cl or Br, the preferred halogen atom being Cl) or an acetyl, (4-chlorophenyl)hydroxymethyl, 4-chlorobenzoyl or 2-(4-chlorobenzamido)ethyl group and R_2 represents a C_1-C_4 alkyl group in which the hydrocarbon chain is linear or branched, the reaction V+VI being carried out without a solvent.

9 Claims, No Drawings

METHOD FOR THE PREPARATION OF FIBRATES

The present invention relates to a novel method for the preparation of fibrates.

The term "fibrates" denotes a family of compounds which have hypocholesterolemic and hypolipidemic properties and correspond to the general formula:



(I$_o$)

in which R'_1 represents especially a halogen atom or a 2,2-dichlorocyclopropyl group, a (4-chlorophenyl)hydroxymethyl group, a 4-chlorobenzoyl group or a 2-(4-chlorobenzamido)ethyl group and R_o represents a hydrogen atom or a branched or unbranched C_1-C_4 alkyl group.

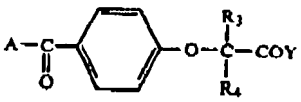
Particularly well-known members of this family are (i) clofibrate, which has the nomenclature: ethyl ester of 4-chlorophenoxy-2-methylpropanoic acid or ethyl 2-(4-chlorophenoxy)-2-methylpropanoate, and (ii) fenofibrate, which has the nomenclature: 1-methylethyl ester of 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid or isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate.

It is known that various methods for the synthesis of fibrates have already been recommended in the past. British Pat. No. GB -A-860 303, which relates to the preparation of clofibrate, proposes the reaction of a phenol of the formula 4-ClC_6H_4OH with an acetone/chloroform mixture in the presence of sodium hydroxide, followed by esterification of the resulting acid with ethyl alcohol.

British Pat. No. GB -A-1 415 295, which relates to the preparation of fenofibrate, proposes a method analogous to that of the above-mentioned British Pat. No. GB -A-860 303 and comprising the following steps:

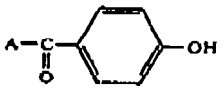
(a) reaction of an acetone/chloroform mixture with (4-chlorophenyl)(4-hydroxyphenyl)methanone,
(b) conversion of the acid obtained according to the said reaction into the acid chloride, and then
(c) esterification of the said acid chloride by reaction with isopropyl alcohol.

Furthermore, British Patent No. GB - A-1 539 897 indicates that it is possible to obtain the compounds of the formula:



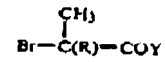
(II)

in which, in particular, A is a phenyl radical substituted by a halogen atom, R_3 and R_4, which are identical or different, each represent the hydrogen atom or an alkyl group and Y represents a hydroxyl group or an alkoxy group, either by the so-called "acetone/chloroform" method using the said acetone/chloroform mixture, or by condensation of a substituted phenol of the formula:



(III)

with a bromine derivative of the formula:



(IV)

in an appropriate solvent.

Depending on the nature of the group R which it is desired to obtain in the final product, especially starting from the 2-bromopropanoic acid derivative of the above formula IV containing the said group R, it is more particularly recommended in British Pat. No. GB - A-1539 897:

(i) not to use the reaction III + IV when R is CH_3, but to use the so-called "acetone/chloroform" method in order to obtain a 2-phenoxy-2-methylpropanoic acid derivative belonging to the fibrate group of compounds, and

(ii) to use the reaction III + IV when R is H in order to obtain a 2-phenoxypropanoic acid derivative, the said reaction of the phenol III with the bromine derivative IV being carried out in an organic solvent such as ethanol or methyl isobutyl ketone, in the presence of K_2CO_3.

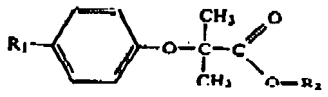
Thus, according to the description in British Pat. No. GB -A-1 539 897, ethyl 2-[4-(4-chlorobenzoyl)phenoxy]propionate is obtained with a yield fo 76% when ethyl 2-bromopropanoate (i.e. the compound of the formula IV in which R = H and Y = OCH_2CH_3) is reacted in approximately molar proportions with (4-chlorophenyl)(4-hydroxyphenyl)methanone (i.e. the compound of the formula III in which A is 4-ClC_6H_4 and which also corresponds to the nomenclature: 4-(4-chlorobenzoyl)(phenol) in methyl isobutyl ketone, in the presence of K_2CO_3.

Austrian Pat. No. AT -A-367 390 has furthermore disclosed a method for the preparation of 2-(3-phenoxyphenoxy)propanoic acid derivatives, in which the phenyl groups are substituted especially by halogen atoms, by a solventless reaction mechanism. In particular, according to Austrian Pat. No. AT - A-367 390, methYl 2-{[6-chloro-3-(2,4-dichlorophenoxy)]phenoxy}propanoate is prepared by the solventless reaction of 6-chloro-3-(2,4-dichlorophenoxy)phenol with methyl 2-bromopropanoate in the presence of K_2CO_3. Comparison of the yields of this reaction carried out with a solvent (methanol) [yield: 76%], according to the teaching of British Pat. No. GB - A-1 539 897, or without a solvent [yield: 72%], according to Austrian Pat. No. AT - A-367 390, shows that there are no significant differences between the solvent technique and the solventless technique.

According to the invention, a novel technique is recommended for solving the problem of fibrate synthesis. This technique, which leads to appreciably higher yields than the closest prior art, surprisingly contradicts firstly the teaching of British Pat. No. GB -A-1 539 897 by involving the reaction of a bromine derivative of the formula IV in which R is CH_3 with a phenol of the formula III in the absence of a solvent, and secondly the

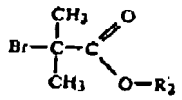
teaching of Austrian Pat. No. AT - A-367 390 by significantly improving the yields.

The method according to the invention for the preparation of a fibrate of the formula:



(I)

in which R_1 represents especially a halogen atom (in particular F, Cl or Br, the preferred halogen being Cl), an acetyl group, a (4-chlorophenyl)hydroxymethyl group of the formula $4\text{-}ClC_6H_4CH(OH)$, a 4-chlorobenzoyl group or a 2-(4-chlorobenzamido)ethyl group and R_2 represents a C_1–C_4 alkyl group with a linear or branched hydrocarbon chain, comprises reacting an excess, relative to the stoichiometric conditions, of an alkyl 2-bromo-2-methylpropanoate of the formula:



(V)

in which R_2 is defined as indicated above, with a substituted phenol of the formula:

(VI)

in which R_1 is defined as indicated above, in the absence of a solvent and in the presence of an excess of K_2CO_3, relative to the stoichiometric conditions, at a temperature greater than or equal to 120° C., for at least 2 hours.

In one embodiment of this method, the resulting fibrate is isolated from the reaction medium directly by precipitation, extraction or distillation.

In another embodiment, the reaction medium containing the fibrate produced by the reaction V+VI is treated with a strong acid (especially HCl or H_2SO_4) to neutralize the excess K_2CO_3, and the fibrate thus obtained is then isolated from the resulting reaction medium by precipitation, extraction or distillation.

The fibrate obtained by the method of the invention is isolated by carrying out one of the following operations: (i) precipitation if the said fibrate is a solid (as in the case of fenofibrate and its analogs of the formula I above), or (ii) extraction with an appropriate solvent or distillation if the said fibrate is liquid or oily (as in the case of clofibrate).

The stoichiometric conditions correspond to the reaction of 1 mol of VI with 1 mol of V in the presence of 0.5 mol of K_2CO_3. As indicated above, the reaction VI+V is carried out in such a way that the bromine derivative V and K_2CO_3 are in excess relative to the said stoichiometric conditions. Advantageously, 1 mol of substituted phenol of the formula VI will be reacted with about 1.7 to about 2.3 mol of derivative of the formula V in the presence of about 0.8 to about 1.8 mol of K_2CO_3, at a temperature of 120°to 160° C., for 3 to 6 hours.

Where appropriate, the neutralization of the excess K_2CO_3 with a strong acid is carried out at a temperature not exceeding 120° C. and preferably at a temperature of the order of 100° C. The strong acid is advantageously a mineral acid such as HCl or, preferably, H_2SO_4.

To summarize, the method according to the invention for the preparation of an ester of the formula I comprises the following two or three steps:

(1) about one mol of VI is reacted with about 1.7 to about 2.3 mol of V (preferably about 2 mol of V), in the absence of a solvent and in the presence of about 0.8 to about 1.8 mol of K_2CO_3 (preferably about 1 mol of K_2CO_3), at a temperature of 120° C. to 160° C. (preferably at a temperature of 140° C. to 145° C.), for at least 2 hours (preferably for 3 to 6 hours),

(2) where appropriate, the excess K_2CO_3 is neutralized with a strong acid at a temperature below 120° C., and

(3) the fibrate is isolated from the reaction medium by precipitation at a temperature below 60° C., by extraction or by distillation.

The best mode which is recommended for the preparation of fenofibrate by the method according to the invention, consists in:

(a) reacting about 1 mol of VI in which R_1 is the 4-chlorobenzoyl group with about 2 mol of V in which R_2 is the isopropyl group, in the absence of a solvent and in the presence of about 1 mol of K_2CO_3, at a temperature of about 140° C. to about 145° C., for about 5 hours,

(b) after the addition of aqueous isopropanol to the resulting reaction medium, neutralizing the excess K_2CO_3 with sulfuric acid at a temperature of the order of 100° C.,

(c) cooling the reaction medium to a temperature of between 15 and 25° C. and collecting the precipitate of fenofibrate by filtration,

(d) washing the precipitate of fenofibrate collected in this way with sodium hydroxide and water in succession, and

(e) recrystallizing the fenofibrate from aqueous isopropanol.

The method according to the invention is also applicable to the preparation of fibrates which, like bezafibrate, have a carboxylic acid group, R_2=H, instead of a carboxylate group. However, in view of the yield of the reaction phenol VI+bromine derivative V in which R_2 is H, the operation is preferably carried out in two stages, namely: preparation of the corresponding ester, by the method of the invention, from a bromine derivative V in which R_2 is an alkyl group, followed by saponification of the said ester to give the desired acid.

Table I which follows summarizes the results of the comparative experiments which were undertaken to demonstrate the value of the method of the invention (Ex. 1) for the solventless reaction V+VI, relative to the use of the same reaction with a solvent (CP1-CP4), according to the teaching of British Pat. No. GB - A-1 539 897, for the synthesis of fenofibrate. For convenience, Table I also shows the yields of the preparation of fenofibrate by the so-called "acetone/chloroform" method (CP6) and of ethyl 2-[4(4-chlorobenzoyl)-phenoxy](CP5) according to the reaction III+IV in which R is H, in the presence of a solvent. The solvents used in comparative examples CP1 and CP2 are those mentioned specifically in British Pat. No. GB - A-1 539 897 and the solvents used in comparative examples CP3 and CP4 are included in the teaching of British Pat. No.

GB - A-1 539 897, although they are not specifically illustrated by examples in the said document.

The invention will be understood more clearly from the following description of an example of preparation by the method recommended here, and comparative examples according to the closest prior art (British Pat. No. GB - A-1 539 897), for the preparation of fenofibrate, as well as examples for the preparation of other fibrates.

PREPARATION I (Example 1)

Preparation of the 1-methylethyl ester of 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibrate)

465 g (2 mol) of (4-chlorophenyl)(4-hydroxyphenyl)-methanone and 815 g (3.9 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid (alternative nomenclature: isopropyl 2-bromo-2-methylpropanoate) are introduced into a 4 liter reactor equipped with a stirrer and a condenser. The medium is heated to 120° C. and 265 g (1.92 mol) of potassium carbonate are then added with the aid of a funnel for solids. The reaction medium is subsequently heated for 5 hours at 140°-145° C. and then cooled to about 100° C. It is subsequently diluted with aqueous isopropyl alcohol and then acidified with sulfuric acid. The reaction medium is then cooled to 18°-20° C. in order to crystallize the product, which is filtered off and washed with sodium hydroxide solution and then water. The product is recrystallized from isopropanol to give 605 g of fenofibrate (yield = 83.9%) with a purity greater than 99.5% (determination by high pressure liquid chromatography, abbreviated to HPLC).

PREPARATION II (Comparative Example CP 1)

46.5 g 0.2 mol) of (4-chlorophenyl)(4-hydroxyphenyl)methanone, 35 g (0.25 mol) of potassium carbonate and 400 ml of 4-methylpentan-2-one (alternative nomenclature: methyl isobutyl ketone) are introduced into a 1 liter 3-necked round-bottomed flask equipped with a stirrer and a condenser. The mixture is heated under reflux for 2 hours in order to form the potassium salt of (4-chlorophenyl)(4-hydroxyphenyl)methanone, after which 41.8 g (0.2 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are added. The mixture is heated under reflux for 12 hours. After cooling, the insoluble inorganic salts are filtered off and the filtrate is concentrated under reduced pressure. The resulting residue is taken up with ethyl ether and washed with 4% sodium hydroxide solution and then water. After the solvent has been evaporated off, the residue is recrystallized from isopropyl ether to give 20 g of fenofibrate (yield = 27.7%).

PREPARATION III (Comparative Example CP 2)

200 ml of anhydrous ethanol are introduced into a 500 ml 3-necked round-bottomed flask equipped with a stirrer and a condenser. 4.6 g (0.2 gram atom) of sodium are then added in portions. When all the sodium has dissolved, 46.5 g (0.2 mol) of (4-chlorophenyl)(4-hydroxyphenyl)methanone are added and the mixture is heated under reflux for 30 minutes. 41.8 g (0.2 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are then added and the mixture is heated under reflux for 8 hours. After concentration, the reaction medium is treated in the same way as in Preparation II. Recrystallization gives 25 g of fenofibrate (yield = 34.7%).

PREPARATION IV (Comparative Example CP 3)

1 liter of isopropyl alcohol, 232.5 g (1 mol) of (4-chlorophenyl)(4-hydroxyphenyl)methanone, 138 g (1 mol) of potassium carbonate and 355 g (1.7 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are introduced into a 4 liter reactor equipped with a stirrer and a condenser. The reaction medium is heated gently, with vigorous stirring, and then kept under reflux for 8 hours. About 400 ml of isopropyl alcohol are then distilled off, after which the medium is cooled, with stirring. The precipitate formed is filtered off and then washed with water in the heterogeneous phase, with shaking. It is filtered off and then washed again with 2% sodium hydroxide solution and then with water until the washings are neutral. The product is filtered off and purified by recrystallization from isopropyl alcohol to give 140 g of fenofibrate (yield = 38.8%).

PREPARATION V (Comparative Example CP 4)

300 ml of dimethylformamide, 100 g (0.43 mol) of (4-chlorophenyl)(4-hydroxyphenyl)methanone and 68.2 g (0.49 mol) of potassium carbonate are introduced into a 1 liter 3-necked round-bottomed flask. The mixture is heated at the reflux temperature of the solvent for 0.5 h, with vigorous stirring, and 120 g (0.57 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are then added. The mixture is kept under reflux for 4 hours. After cooling, the reaction medium is hydrolyzed with water and then extracted with chloroform. The organic phase is subsequently washed with 3% by weight sodium hydroxide solution and then with water until the washings are neutral. The residue obtained after the solvent has been evaporated off is recrystallized from isopropyl alcohol to give 30 g of fenofibrate (yield = 19.3%).

PREPARATION VI (Example 1)

Preparation of the 1-methylethyl ester of 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibrate)

100 g (0.43 mol) of (4-chlorophenyl)(4-hydroxyphenyl)methanone and 165 g (0.79 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are introduced, under a nitrogen atmosphere, into a 3-necked round-bottomed flask equipped with a stirrer and a condenser. The reaction medium is heated to 110° C. and a solution of 50 g (0.36 mol) of potassium carbonate in 50 ml of demineralized water is then added slowly over a period of 20 minutes, with distillation taking place at 100° C. The distillate separates out into 2 phases. The lower phase is recycled into the reaction medium. After heating at 110°-112° C. for 1.5 h, the reaction medium is brought to 140° C. and a temperature of 140°-145° C. is maintained for 4 hours. The reaction medium is then cooled to about 90° C. and 210 ml of 80% isopropyl alcohol are added. The mixture is then left to cool for 12 h, with stirring, after which the suspension obtained is filtered at 0° C. The precipitate is washed with 4 times 200 ml of demineralized water and then recrystallized from propan-2-ol to give 119.5 g (yield = 77%) of fenofibrate.

PREPARATION VII (Example 2)

Preparation of 2-{4-[2-(4-chlorobenzoylamino)ethyl]-phenoxy}-2-methylpropanoic acid (bezafibrate)

(1) 27.5 g (0.1 mol) of 4-[N-(4-chlorobenzoyl)-2-aminoethyl]phenol and 38 g (0.18 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are introduced, under a nitrogen atomosphere, into a 500 ml roundbottomed flask equipped with a stirrer and a condenser. The reaction medium is heated to 135° C. and 20 g (0.145 mol) of potassium carbonate are then added slowly. The temperature is raised to 140°-145° C. for 4 h, with stirring. 5 g (0.024 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid and 5 g (0.036 mol) of potassium carbonate are then added. The reaction medium is kept at 145° C. for 1 h and then cooled to 100° C. 100 ml of propan-2-ol are added, with vigorous stirring, followed by a mixture of 80 ml of propan-2-ol, 6 ml of sulfuric acid and 30 ml of water. The mixture is left to cool and the precipitate formed is filtered off. 43 g of product are obtained by successively forming a paste with 1% sodium hydroxide solution and then washing with water until the washings are neutral. This product is recrystallized from 90% propan-2-ol to give 36.4 g (yield=90%) of the 1-methylethyl ester of 2-{4-[2-(4-chlorobenzoylamino)ethyl]phenoxy}-2-methylpropanoic acid melting at 84° C.

(2) 36 g the ester obtained above are hydrolyzed with 4.25 g of sodium hydroxide in 130 ml of methanol, at 50° C., for 1 h. After concentration, the residue is taken up with water. The aqueous phase is washed with ether and then acidified in the cold. The expected acid precipitates. The precipitate is filtered off, washed with water and dried to give 26 g (yield=80%) of bezafibrate melting at 183° C.

PREPARATION VIII (Example 3)

Preparation of 2[-4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid (ciprofibrate)

(1) 1500 g (11 mol) of methyl-(4-hydroxyphenyl)methanone and 3800 g (18.2 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid are introduced into a 6 l reactor under a nitrogen atmosphere. The mixture is heated to 120° C. and 1300 g (9.4 mol) of potassium carbonate are added slowly. A mixture of water and organic products distils off. The temperature is raised to 140° C. After 1 hour, 350 g (1.7 mol) of the 1-methylethyl ester of 2-bromo-2-methylpropanoic acid and then 222 g (1.6 mol) of potassium carbonate are added. The temperature is kept at 140° C. for 1 hour and then lowered to 80° C. 4 liters of propan-2-ol are then added and the mixture is left to cool, with stirring. The insoluble inorganic salts are filtered off and the filtrate is concentrated under reduced pressure. The residue is taken up with ethyl acetate and washed with 10% sodium hydroxide solution and then water. The organic phase is dried and concentrated and the oil obtained is distilled at 136°-138° C. under 0.5 mm of mercury to give 2350 g (yield=81%) of the 1-methylethyl ester of 2-(4-acetylphenoxy)-2-methylpropanoic acid.

(2) 2350 g (8.9 mol) of the ester obtained above and 3 liters of methanol are introduced into a 10 liter reactor under a nitrogen atmosphere. The reaction medium is cooled to 0° C. and 576.5 g (10.68 mol) of potassium borohydride are added slowly, with vigorous stirring. Stirring is maintained for 12 h at room temperature and the mixture is then concentrated under reduced pressure. The residue is treated with iced water and taken up with ethyl acetate. After washing with water, the organic phase is dried and concentrated to give 2355 g yield=99.5%) of the 1-methylethyl ester of 2-[4-(1-hydroxyethyl phenoxy]-2-methylpropanoic acid in the form of a colorless oil.

(3) 240 ml of chloroform, 120 g (0.453 mol) of the ester obtained above and 3 ml of dimethylformamide are introduced into a 1 liter round-bottomed flask under a nitrogen atmosphere. The mixture is cooled to 0° C. and a solution of 18 ml of phosphorus tribromide in 50 ml of chloroform is then introduced, with stirring. The temperature is kept at 0° C. for 1 h. The reaction medium is then stirred at 30° C. for 1 h, after which 84 g of triethylamine are added. The mixture is heated under reflux for 8 h and then cooled and hydrolyzed on ice. It is extracted with chloroform and the mixture is filtered. After the organic phase has been washed with water and then dried, it is concentrated under reduced pressure to give 105 g (yield=93%) of the 1-methylethyl ester of 2-(4-ethenylphenoxy)-2-methylpropanoic acid.

(4) 5 g of the ester obtained above, 12 ml of chloroform and then 0.5 g of benzyltriethylammonium chloride are introduced into a 100 ml round-bottomed flask. 12 g of sodium carbonate are then added dropwise, after which the mixture is heated at 40° C. for 5 h. The reaction medium is subsequently cooled, hydrolyzed and then extracted with chloroform. After washing with water, the organic phase is dried and concentrated under reduced pressure to give 5 g (yield=75%) of the 1-methylethyl ester of 2-[4-(2,2-dichlorocyclopropyl)-phenoxy]-2-methylpropanoic acid in the form of an oil.

(5) 5 g of the ester obtained above, 20 ml of methanol and 0.84 g of sodium hydroxide are introduced into a 100 ml round-bottomed flask. The mixture is heated at 50°-60° C. for 2 h, with stirring and then concentrated under reduced pressure. The solid obtained is taken up with water and the aqueous solution is washed with ether and then acidified to pH 1 with hydrochloric acid. Extraction is carried out with ethyl acetate. The organic phase is washed with water and then dried and concentrated. The oil obtained crystallizes on the addition of cyclohexane. The solid obtained is recrystallized from toluene to give 3.6 g (yield=82%) of ciprofibrate melting at 115° C.

Preparations I-VIII given above to illustrate the invention and the comparative examples show that the method according to the invention affords the following advantages:

(i) very high yields (83.9%) compared with the prior art involving a solvent (19% to 39%);
(ii) products with the very high purity required in the preparation of a drug;
(iii) an energy saving by reducing the reaction times (essentially reducing the heating times);
(iv) solvent use restricted to crystallizations; and
(v) a larger operating unit for the same volume of reactor.

The method according to the invention is directly applicable on the industrial scale

Example	Method (Preparation)
Ex. 1	A (I)
CP 1	B (II)
CP 2	B (III)
CP 3	B (IV)
CP 4	B (V)
CP 5	C
CP 6	D ("acet

NOTES
(a) Method:
A: according to th
the absence of a w
B: according to th
with $BrC(CH_3)_2C$
C: according to th
with $BrCH(CH_3)C$
D: according to th
VI with an acetone
acid.
(b) Ethyl 2-[4-(4-cl
(c) The overall yie
obtained with a yi
phenol VI) and the

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TABLE I

Example	Method (a) (Preparation)	Solvent	Product obtained	Yield (%)
Ex. 1	A (I)	—	fenofibrate	83.9
CP 1	B (II)	$CH_3COCH_2CH(CH_3)_2$	fenofibrate	29.7
CP 2	B (III)	CH_3CH_2OH	fenofibrate	34.7
CP 3	B (IV)	$CH_3CHOHCH_3$	fenofibrate	38.8
CP 4	B (V)	$HCON(CH_3)_2$	fenofibrate	19.3
CP 5	C	CH_3CH_2OH	(b)	70
CP 6	D ("acetone/chloroform")		fenofibrate	≈70 (c)

NOTES

(a) Method:

A: according to the invention by reaction of VI with $BrC(CH_3)_2COOCH(CH_3)_2$ in the absence of a solvent;

B: according to the teaching of British Patent GB - A-1 539 897 by reaction of VI with $BrC(CH_3)_2COOCH(CH_3)_2$ in the presence of a solvent;

C: according to the teaching of British Patent GB - A-1 539 897 by reaction of VI with $BrCH(CH_3)COOCH_2CH_3$ in the presence of a solvent;

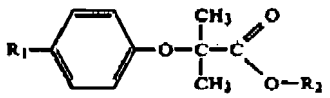
D: according to the teaching of British Patent GB - A-1 539 897 by (i) reaction of VI with an acetone/chloroform mixture, then (ii) esterification of the corresponding acid.

(b) Ethyl 2-[4-(4-chlorobenzoyl)phenoxy]propionate

(c) The overall yield of method D is about 70%; more precisely, fenofibric acid is obtained with a yield of 85% (this acid contains 3 to 4% by weight of unreacted phenol VI) and the esterification is then carried out with a yield of 85%.

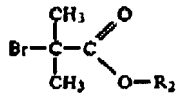
What is claimed is:

1. A method for the preparation of a substance selected from the group comprising the fibrates corresponding to the general formula:



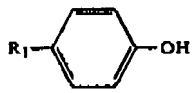
(I)

in which R_1 represents especially a halogen atom (in particular F, Cl or Br, the preferred halogen atom being Cl) or an acetyl, (4-chlorophenyl)hydroxymethyl, 4-chlorobenzoyl or 2-(4-chlorobenzamido)ethyl group and R_2 represents a C_1–C_4 alkyl group in which the hydrocarbon chain is linear or branched, which comprises reacting an excess, relative to the stoichiometric conditions, of an alkyl 2-bromo-2-methylpropanoate of the formula:



(V)

in which R_2 is defined as indicated above, with a substituted phenol of the formula:



(VI)

in which R_1 is defined as indicated above, in the absence of a solvent and in the presence of an excess of K_2CO_3, relative to the stoichiometric conditions, at a temperature greater than or equal to 120° C., for at least 2 h.

2. The method according to claim 1, wherein the resulting fibrate is isolated from the reaction medium by precipitation, extraction or distillation.

3. The method according to claim 1, wherein the reaction medium containing the resulting fibrate is treated with a strong acid to neutralize the excess K_2CO_3, and the fibrate is then isolated from the reaction medium by precipitation, extraction or distillation.

4. The method according to claim 1, wherein 1 mol of VI is reacted with about 1.7 to about 2.3 mol of V in the presence of about 0.8 to about 1.8 mol of K_2CO_3, at a temperature of 120°to 160° C., for 3 to 6 hours.

5. The method according to claim 1, wherein 1 mol of VI is reacted with about 2 mol of V in the presence of about 1 mol of K_2CO_3, at a temperature of 140°to 145° C.

6. The method according to claim 3, wherein the neutralization of the excess K_2CO_3 is carried out with sulfuric acid at a temperature not exceeding 120° C. and preferably of the order of 100° C.

7. The method according to claim 1, wherein:

(1) about one mol of VI is reacted with about 1.7 to about 2.3 mol of V (preferably about 2 mol of V) in the absence of a solvent and in the presence of about 0.8 to about 1.8 mol of K_2CO_3 (preferably about 1 mol of K_2CO_3, at a temperature of 120° C. to 160° C. (preferably at a temperature of 140° C. to 145° C.), for at least 2 hours (preferably for 3 to 6 hours),

(2) the excess K_2CO_3 is neutralized with a strong acid at a temperature below 120° C., and

(3) the fibrate is isolated from the reaction medium by precipitation at a temperature below 60° C., or by extraction or distillation.

8. The method according to claim 1 for the preparation of fenofibrate, wherein:

(a) about 1 mol of VI in which R_1 is the 4-chlorobenzoyl group is reacted with about 2 mol of V in which R_2 is the isopropyl group, in the absence of a solvent and in the presence of about 1 mol of K_2CO_3, at a temperature of about 140° C. to about 145° C., for about 5 hours,

(b) after the addition of aqueous isopropanol to the resulting reaction medium, the excess K_2CO_3 is neutralized with sulfuric acid at a temperature of the order of 100° C.,

(c) the resulting reaction medium is cooled to a temperature of between 15 and 25° C. and the precipitate of fenofibrate is collected by filtration,

(d) the precipitate filtered off in this way is washed with sodium hydroxide followed by water, and then

(e) the fenofibrate is recrystallized from aqueous isopropanol.

9. The method of preparation according to claim 1 for the synthesis of a fibrate of the formula I in which R_2=H, wherein the corresponding ester is prepared, according to the method of claim 1, by reacting the substituted phenol VI with an alkyl 2-bromo-2-methylpropanoate of the formula V in which R_2 is a C_1–C_4 alkyl group, in the absence of a solvent, and the resulting ester is then saponified.

* * * * *

EXHIBIT III

MAINTENANCE FEE PAYMENT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
003047

MAX FOGIEL
61 ETHEL ROAD WEST
PISCATAWAY, NJ 08854

DATE MAILED
10/28/91

173178

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,739,101	173	830	----	07/043,184	04/19/88	04/27/87	04	NO	PAID

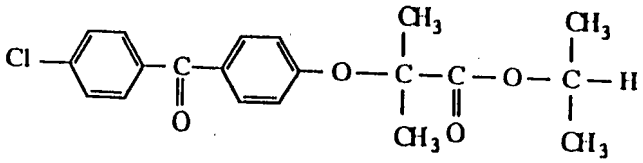
EXHIBIT IV

PACKAGE INSERT

LIPIDIL®
(Fenofibrate Capsules)

DESCRIPTION

LIPIDIL (fenofibrate capsules) is a lipid regulating agent. It is available as capsules for oral administration. Each capsule contains 100 mg of fenofibrate. Each capsule also contains lactose, NF; magnesium stearate, NF; and pregelatinized starch, NF. The chemical name is 2-(4-(4-chlorobenzoyl) phenoxy)-2-methylpropanoic acid 1 methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}ClO_4$ and the molecular weight is 360.84; fenofibrate is insoluble in water. The melting point is 77-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

The effects of LIPIDIL 100 mg tid on serum triglycerides were studied in two randomized, double-blind clinical trials[1]. 147 hypertriglyceridemic patients (Types IV and V) were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 250 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with LIPIDIL decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol as seen in the following table of changes seen at the end of treatment in patients with triglycerides of 500 to 1500 mg/dL.

Changes in Lipid and Lipoprotein Determinations: Type IV/V Patients

	Placebo		LIPIDIL (100 mg tid)		
	Baseline Mean (mg/dL)	% Change	Baseline Mean (mg/dL)	% Change	Net Difference (of %)
Triglycerides					
Total	710	+ 7	726	- 55	- 62
VLDL	537	+ 19	543	- 51	- 70
Cholesterol					
Total	272	0	261	- 14	- 14
HDL	27	+ 5	30	+ 23	+ 18
LDL	100	- 4	103	+ 45	+ 49
VLDL	137	+ 11	126	- 49	- 60

The mechanism of action of LIPIDIL has not been clearly established in man. Fenofibric acid, the active metabolite of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglyceride-rich lipoprotein (i.e., VLDL). LIPIDIL also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single radiolabelled 300 mg dose of fenofibrate appeared in the urine primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration, and the compound is eliminated with a half-life of 20 hours. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with 100 mg/day, and did not demonstrate accumulation across time following multiple dose administration. In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of 100 mg was 1.2 L/h, which compares with 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

In a study in patients with severe renal impairment (creatinine clearance < 50 ml/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage.

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However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 ml/min) the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults. Therefore, the dosage of LIPIDIL should be reduced in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

INDICATIONS AND USAGE

LIPIDIL (fenofibrate capsules) is indicated as adjunctive therapy to diet for treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who are at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to present a risk of pancreatitis. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention. LIPIDIL therapy may be considered for those subjects with triglyceride elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of LIPIDIL therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

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Because the benefit/risk ratio of LIPIDIL (fenofibrate) has not been established in clinical trials of primary or secondary prevention to reduce the risk of developing coronary heart disease, LIPIDIL is not indicated for such use. (See WARNINGS and PRECAUTIONS).

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

2. Preexisting gallbladder disease (see WARNINGS).

3. Hypersensitivity to fenofibrate.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between LIPIDIL (fenofibrate), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to LIPIDIL. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In a study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed 1 year beyond. There was a statistically significant, 44% higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

   During the 5 year primary prevention component of the Helsinki Heart Study involving 4081 middle-aged males treated with either gemfibrozil or placebo, and the 3.5 year open extension, total mortality was 22% higher in the original gemfibrozil randomization group (p=0.19, 95% confidence interval for relative risk G:P=0.91-1.64). Cancer deaths trended higher in the gemfibrozil group (p=0.11), while cancers (excluding basal cell carcinoma) were diagnosed in 2.5% of patients in both treatment groups. Because of the more limited size of the Helsinki

Heart Study, the relative risk of death from any cause did not differ statistically from the relative risk of 1.29 clofibrate/placebo observed at the 9 year follow-up of the WHO study. Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group (0.9% vs. 0.5% with placebo) did not differ statistically from the excess observed in the clofibrate group compared to placebo in the WHO study.

The secondary prevention component of the Helsinki Heart Study involved 628 middle-aged males excluded from the primary prevention study because of known or suspected coronary heart disease and treated with either gemfibrozil or placebo for 5 years. Cardiac deaths trended higher in the gemfibrozil group (17/311 vs. 8/317 placebo patients, p=0.06, hazard ratio 2.2, 95% confidence interval for hazard ratio = 0.94-5.05). Gallbladder surgery was more frequent in the gemfibrozil group (1.9% vs. 0.3%, p=0.07), as was appendectomy (6 cases on gemfibrozil vs. 0 on placebo, p=0.029).

2. Liver Function: Fenofibrate use at doses of 200 to 300 mg/day is associated with significant increases in serum transaminases [AST (SGOT) or ALT (SPGT)]. Increases to > 3 times the upper limit of normal occurred in 6.3% of LIPIDIL-treated patients taking 200 to 300 mg/day in controlled multiple-dose trials lasting 8-24 weeks.

Patients with AST or ALT > 3x the Upper Normal Limits in Controlled Clinical Trials vs Fenofibrate (200 to 300 mg/day)

	N	# Events	Events Rate
Control	336	4	1.2%
Fenofibrate	442	28	6.3%

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. However, the transaminase determinations remained above normal limits in 2 of the 28 patients (7.1%) at the end of follow-up off treatment. Fenofibrate hepatotoxicity appears to be dose-related. In an 8-week dose-ranging study the incidence of ALT or AST elevations at least three times the upper limit of normal was 13% in patients receiving 200 or 300 mg/day and was 0% in those receiving 100 or 50 mg/day, or placebo. Both hepatocellular and cholestatic hepatitis have been reported. In literature reports, hepatitis associated with fenofibrate has occurred after exposures of weeks to several years.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed

for the duration of therapy with LIPIDIL, and therapy discontinued if enzyme levels persist above three times the normal limit.

3. Cholelithiasis. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the gemfibrozil treatment group. Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LIPIDIL therapy should be discontinued if gallstones are found.

4. Concomitant Oral Anticoagulants. Caution should be exercised when anticoagulants are given in conjunction with LIPIDIL because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with LIPIDIL and HMG-CoA reductase inhibitors (such as lovastatin, pravastatin, and simvastatin). No data exists on this combined therapy. The association of the chemically and pharmacologically related similar compound gemfibrozil and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

   In virtually all patients who have had an unsatisfactory lipid response to either drug alone, any potential lipid benefit of combined therapy with HMG CoA reductase inhibitors and LIPIDIL does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. The use of fibrates alone, including LIPIDIL, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving LIPIDIL and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, LIPIDIL therapy should be stopped.

6. The effect of LIPIDIL on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. LIPIDIL should be administered only to those patients described under INDICATIONS AND USAGE. If a significant reduction in fasting chylomicronemia does not occur, LIPIDIL should be discontinued.

PRECAUTIONS

1. **Initial therapy:** Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting LIPIDIL therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

2. **Continued therapy:** Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of LIPIDIL. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 300 mg/day.

3. **Pancreatitis** has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy or a secondary phenomenon through biliary tract stone or sludge formation and obstruction of the common bile duct.

4. **Hypersensitivity Reactions:** Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with LIPIDIL. Urticaria was seen in 1.25 vs 0%, and rash in 2.82 vs 1.23% of fenofibrate and placebo patients respectively in controlled trials.

5. **Hematologic Changes:** Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of LIPIDIL therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of LIPIDIL administration.

6. **Skeletal muscle:** The use of fibrates alone, including LIPIDIL may occasionally be associated with myositis. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatinine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

7. **Drug interactions:**

(A) Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPIDIL. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

(B) HMG-CoA reductase inhibitors: Rhabdomyolysis has occurred when lovastatin was administered in combined therapy with gemfibrozil, a compound of the fibrate class related to fenofibrate. In most patients who have had an unsatisfactory lipid response to either drug alone, any possible benefit of combined therapy with an HMG-CoA reductase inhibitor and LIPIDIL is not outweighed by the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(C) Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take LIPIDIL at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

(D) Cyclosporin: Because cyclosporin can produce nephrotoxicity with decrease in creatine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including LIPIDIL, there is a risk that an interaction will lead to deterioration. The benefits and risks of using LIPIDIL with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

8. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum

recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

9. **Pregnancy Category C:** Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

10. **Nursing mothers:** Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

11. **Use in Children:** Safety and efficacy in children have not been established.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 1% or more of patients treated with LIPIDIL during the six month and the eight week double-blind, placebo-controlled trials in the U.S.[1,3] are listed in the table below. Adverse events led to discontinuation of treatment in 6% of patients treated with LIPIDIL and in 2% treated with placebo. Skin rashes were the most frequent events, causing discontinuation of LIPIDIL treatment in 2% of patients in double-blind trials.

BODY SYSTEM Adverse Event	LIPIDIL (N = 191)	PLACEBO (N = 183)
BODY AS A WHOLE		
Asthenia/Fatigue	5%	3%
Infections	18%	15%
Flu Syndrome	5%	2%
Localized/Misc. Pain	8%	7%
Headache	5%	4%
CARDIOVASCULAR		
Arrhythmia	1%	1%
DIGESTIVE		
Dyspepsia	5%	7%
Eructation	1%	0%
Flatulence	3%	2%
Nausea/Vomiting	4%	3%
Abdominal Pain	3%	3%
Constipation	3%	2%
Diarrhea	3%	7%
MUSCULOSKELETAL		
Arthralgia	3%	4%
NERVOUS		
Decreased Libido	2%	1%
Paresthesia	1%	2%
Increased Appetite	1%	1%
Dizziness	2%	1%
Insomnia	1%	1%
RESPIRATORY		
Cough	1%	1%
Rhinitis	4%	3%
Sinusitis	1%	1%
SKIN & APPENDAGES		
Pruritus	3%	1%
Rash	6%	2%
SPECIAL SENSES		
Earache	1%	1%
Eye Floaters	1%	0%
Blurred Vision	1%	1%
Conjunctivitis	1%	2%
Eye Irritation	2%	1%
UROGENITAL		
Polyuria	1%	1%
Vaginitis	1%	1%

Additional clinical adverse events reported by fewer than 1% of patients in the U.S. double-blind studies, those reported in other clinical trials, and spontaneously reported in post-marketing surveillance outside the U.S. are listed below, categorized by causality:

PROBABLY CAUSALLY RELATED: Digestive: hepatitis, cholelithiasis, cholecystitis, hepatomegaly; Musculoskeletal: myalgia, myasthenia, rhabdomyolysis; Skin and appendages: photosensitivity, eczema; Respiratory: allergic pulmonary alveolitis.

CAUSAL RELATIONSHIP NOT ESTABLISHED: Body as a whole: facial edema, weight decrease, fever, epistaxis; Cardiovascular: peripheral edema, angina, palpitations, tachycardia, migraine; Digestive: hematemesis, pancreatitis; Respiratory: congestion; Nervous: dry mouth, vertigo, anxiety, sleep disorders, confusion; Skin and appendages: lupus-like syndrome, ichthyosis, telangiectasis, alopecia; Special senses: amblyopia, tinnitus; Urogenital: decreased male fertility, renal lithiasis.

LABORATORY: In the two U.S. placebo controlled studies, serum transaminase determinations (SGPT and/or SGOT) were increased to over three times the upper normal limit in 8 to 10% of patients taking Lipidil at doses of 300 mg/day (See WARNINGS). Other changes that occurred more frequently during Lipidil treatment compared to placebo included increases in creatinine and blood urea, and decreases in hemoglobin and uric acid.

Additional laboratory findings that have been reported during fenofibrate treatment that are probably causally related include: anemia, leucopenia, eosinophilia, thrombocytopenia, and increased creatinine phosphokinase.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate triglyceride-lowering diet before receiving LIPIDIL, and should continue this diet during treatment with LIPIDIL.

LIPIDIL should be given with meals. The initial dose is usually 100 mg per day, depending on the physician's assessment of the patient's risk for pancreatitis (see INDICATIONS AND USAGE). Dosage should be individualized according to patient response, and should be increased sequentially if necessary following repeat serum triglyceride estimations at 4-to-8 week intervals. The maximum dose is 300 mg/day.

Treatment with LIPIDIL should be initiated at a dose of 100 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and triglyceride levels at this dose. In the elderly, the initial dose should likewise be limited to 100 mg/day.

OVERDOSAGE

Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

LIPIDIL (fenofibrate) is available as opaque white hard gelatin capsules. Each capsule contains 100 mg fenofibrate. Each capsule is printed with "LIPIDIL". LIPIDIL is available in bottles of 90 and bottles of 1000.

NDC 0087-0709-41	Bottles of 90
NDC 0087-0709-03	Bottles of 1000

STORAGE

Store in a cool dry place. Protect from temperatures above 30°C (86°F). Avoid excessive light and humidity.

Distributed by

FOURNIER RESEARCH INC.
689 Mamaroneck Avenue
P.O.Box 340
MAMARONECK
N.Y. 10543

CAUTION--Federal law prohibits dispensing without prescription.

Revised: November 12, 1993

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